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AMENDED SPECIFICATION

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PATENT SPECIFICATION 1 123 770

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NO DRAWINGS

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2-CYANO-3-OXO-STEROIDS

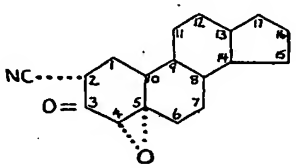
We, STERLING DRUG, INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 90, Park Avenue, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to cyano substituted epoxy steroids, and in particular it is concerned with 2α-cyano-4α,5α-epoxy androstane steroids and the preparation thereof.

Our Patent Specification Nos: 905,845 and 963,442 disclose 2-cyano-3-oxo steroids, the steroid moiety having from 17 to 23 carbon atoms exclusive of ester radicals or a salt thereof, said compounds being prepared by treating the corresponding steroido[2.3-d]-isoxazole with a strong base, and if desired, acidifying the basic salt obtained to obtain the free product.

The present invention is particularly concerned with a novel class of such compounds having particular pharmacological activity, namely 2α - cyano - 4α,5α - epoxy - 3 - oxo-steroids, the steroid moiety having nineteen to twenty-three carbon atoms exclusive of ester radicals.

The ring structure of the compounds of the invention is represented by the following structure:



The exact nature of the steroid moiety is not critical, and it can be derived from any steroid of the general type known to exhibit hormonal or other pharmacological or endocrinological properties. Such steroid moieties have from nineteen to about twenty-three carbon atoms, not counting carbon content which may be provided by esterified hydroxy groups. Esterified hydroxy-steroids are included within the scope of the invention, but the carbon content contributed by the acid moiety of the ester is not considered part of the essential carbon content of the steroid.

The steroid moiety can be any member of the androstane series. The foregoing can contain varying degrees of unsaturation and a variety of substituents in the form of hydrocarbon radicals or functional groups conventionally employed in the steroid art. Representative of the steroid moieties which make up the compounds of the invention are those having at position 17 a hydroxy, acyloxy, oxo, or both a hydroxy and a lower-alkyl or lower alkynyl radical, characteristic of the androgenic and anabolic steroids. The steroid moiety can also have one or more substituents at other positions of the nucleus, for example, hydroxy, acyloxy, or oxo radicals at positions 6, 7, 11, 12, 14 or 16; epoxy groups at adjacent positions, for example at the 9,11-, 11,12- or 15,16-positions; halogen atoms, preferably fluorine, chlorine or bromine, for example, at the 6-, 7-, 9-, 12-, 16- or 17-positions; and lower-alkyl groups, for example, at the 6-, 7-, 11- or 16-positions. The steroid moiety can also have one or more double bonds, for example, at the 6,7-, 9,11- or 16,17-positions. The steroid moiety possesses angular methyl groups at C_{10} and C_{13}.

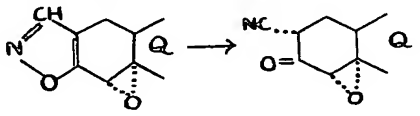
The steroid moieties in the compounds of the invention contain, nineteen carbon atoms plus any carbon content which may be provided by one or more nuclearly substituted carbon containing radicals, up to and including a total of twenty-three carbon atoms, exclusively of ester radicals.

When ester linkages are present in the

steroid molecule, the acyl radicals are preferably derived from carboxylic acids having from one to about ten carbon atoms, conventionally employed in the steroid art, and having a molecular weight less than about 200. Representative of the acyl radicals which can be present are lower-alkanoyl radicals, e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, caproyl, heptanoyl, octanoyl and trimethylacetyl; carboxy-lower-alkanoyl radicals, e.g., succinyl (β-carboxypropionyl); cycloalkyl-lower-alkanoyl radicals, e.g., β-cyclopentylpropionyl and β-cyclohexylpropionyl; monocarbocyclic aroyl radicals, e.g., benzoyl, *p*-toluyl, *p*-nitrobenzoyl and 3,4,5-trimethoxybenzoyl; monocarbocyclic aryl-lower-alkanoyl or -alkenoyl radicals, such as phenylacetyl, β-phenylpropionyl and cinnamoyl; and monocarbocyclic aryloxy-lower-alkanoyl radicals, such as *p*-chlorophenoxyacetyl. Esters of inorganic acids such as phosphoric acid are also contemplated. When monocarbocyclic aryl groups are present in the ester moieties, monocarbocyclic aryl includes phenyl and phenyl substituted by from one to three lower-alkyl, lower-alkoxy, halogen or nitro groups.

The esters are prepared by conventional procedures as by treating the corresponding steroid alcohol with the appropriate acid halide or anhydride.

The 2α - cyano - 4α,5α - epoxy - 3 - oxo steroids of the invention are prepared by cleaving a steroido[2,3 d]isoxazole with a strong base according to the following scheme.

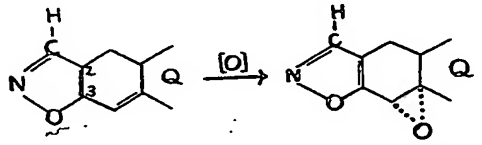


wherein Q represents the remainder of the steroid moiety.

Any strong base can be used for the conversion of the isoxazole to the cyano ketone; however, alkali metal alkoxides are preferred and the reaction is best carried out in an anhydrous medium.

The 2α - cyano - 4α,5α - epoxy - 3 - oxo steroids are acidic in nature, having an active hydrogen atom in the 2-position, and therefore form salts with strong bases such as alkali metal hydroxides or alkoxides. Thus, in the cleavages of the isoxazole a salt of the 2α-cyano - 4α,5α - epoxy - 3 - oxo steroid is initially produced, and said salt is converted to the free 2α-cyano-4α,5α-epoxy-3-oxo steroid by acidification. For the purposes of the present invention the salts are the full equivalents of the free acids (free 2α - cyano - 4α,5α-epoxy-3-oxo steroids).

The intermediate 4α,5α - epoxy - steroids-[2,3-d]isoxazoles are prepared by reacting a $\Delta^{4,5}$-steroido[2,3-d]isoxazole with an oxidizing agent capable of converting an olefinic double bond to an epoxide according to the following equation:



Such oxidizing agents include hydrogen peroxide under alkaline conditions, or a carboxylic peracid, for example, perbenzoic acid, monoperphthalic acid and peracetic acid.

Endocrinological evaluation of the 2α-cyano-4α,5α-epoxy-3-oxo steroids of the invention has shown that they possess adrenocortical inhibiting properties. For example, 2α-cyano-4α,5α - epoxyandrostan - 17β - ol - 3 - one when tested in rats was found to prevent ACTH-induced increases in plasma and adrenal corticosteroids, to prevent ACTH-induced nitrogen loss and thymolysis, and to prevent ACTH and cold stress induction of lower tryptophan pyrrolase activity; and when tested in dogs was found to reverse ACTH-stimulated adrenal hyperactivity and to inhibit adrenal steroidogenesis by blocking adrenal 3β-hydroxy steroid dehydrogenase. These results indicate that the 2α - cyano - 4α,5α - epoxy-3-oxo steroids of the invention are useful in treating such pathological conditions as Cushing's syndrome, adrenal neoplasia, physical trauma, hirsutism, psychic distress and primary and secondary aldosteronism.

The compounds of the invention can be prepared for use by dispersing them in an aqueous suspension or by dissolving them in a pharmacologically acceptable oil or oil-water emulsion for parenteral administration; or by incorporation in tablet form with excipients for oral administration.

The structures of the compounds of the invention were established by the mode of preparation, by elementary analysis and by ultraviolet and infrared spectral data.

The following examples will further illustrate the invention without the latter being limited thereby.

Example 1.

a) 17β - Hydroxy - 4α,5α - epoxyandrostano-[2,3-d]isoxazole.

To a solution of 6.16 g. of 17β - hydroxy-4 - androsteno[2,3-d]isoxazole, 0.5 g. of sodium acetate and 50 ml. of acetic acid in 500 ml. of benzene was added a solution of 3.8 ml. of 42.2% peracetic acid in 10 ml. of acetic acid. The reaction mixture was allowed to stand at room temperature for one day. The solvent was evaporated from the mixture, and the residue was recrystallized first from acetone (yield 4.42 g.) and then from ethanol to give 17β - hydroxy - 4α,5α - epoxyandrostano-[2,3-d]isoxazole, m.p. 205—207°C., $[\alpha]_D^{25}$ = +107.8° (1% in chloroform).

b) 2α - Cyano - 4α,5α - epoxyandrostan - 17β-ol-3-one.

A mixture of 0.40 g. of 17β - hydroxy-

4α,5α - epoxyandrostano[2,3-d]isoxazole, 0.1 g. of sodium methoxide and 10 ml. of tetrahydrofuran was stirred for fifteen minutes. Methonal (5 ml.) was added and the mixture stirred for ten minutes. Water was then added gradually until a turbid solution resulted. The mixture was extracted with benzene and ether, and the aqueous layer was acidified with dilute sulfuric acid. The precipitate which formed was collected, dried and recrystallized from pyridine-dioxane to give 2α - cyano - 4α,5α-epoxyandrostan - 17β - ol - 3 - one, m.p. 258—270°C. (decompn.), $[\alpha]_D^{25} = +137.4°$ (1% in pyridine).

Example 2.

a) 17β - Acetoxy - 4α,5α - epoxyandrostano-[2,3-d]isoxazole.

To a solution of 3.00 g. of maleic anhydride in 150 ml. of methylene dichloride containing a few mg. of sodium acetate was added 0.97 ml. of 88% hydrogen peroxide, followed by 7.1 g. of 17β - acetoxy - 4 - androsteno-[2,3-d]isoxazole and 10 drops of pyridine. The reaction mixture was kept in a refrigerator overnight. The excess peracid was destroyed by adding sodium bisulfite solution, and the mixture was washed with water and with sodium bicarbonate solution. The organic solution was dried and concentrated *in vacuo*. The residue was recrystallized successively from acetone, ethyl acetate (yield, 6.63 g) and benzene-methanol to give 17β - acetoxy-4α,5α - epoxyandrostano[2,3-d]isoxazole, m.p. 228.5—230°C., $[\alpha]_D^{25} = +76.5°$ (1% in chloroform).

b) Treatment of 17β-acetoxy - 4α,5α-epoxyandrostano[2,3-d]isoxazole with sodium methoxide according to the procedure of Example 1, part (b) led to a separable mixture of 2α - cyano - 4α,5α - epoxyandrostan - 17β-ol-3-one and its acetate, 17β - acetoxy - 2α-cyano - 4α,5α - epoxyandrostan - 3 - one, colorless needles, m.p. 195—198° C. when recrystallized from a benzene-acetone mixture; $[\alpha]_D^{25} = +116.2°$ (1% in pyridine), − 21.2° (1% in chloroform).

Example 3.

a) 4α,5α - Epoxy - 17β - hydroxy - 17α-ethynylandrostano[2,3 - d] - isoxazole, m.p. 237.0—243.0°C. (dec.) (corr.) (recrystallized from dioxane-tetrahydrofuran-acetone), $[\alpha]_D^{25} = +32.0°$ (1% in chloroform), was prepared by treating 17β - hydroxy - 17α-ethynyl - 4 - androsteno[2,3 - d]isoxazole with maleic anhydride and hydrogen peroxide in methylene dichloride solution.

b) 2α-Cyano-4α,5α-epoxy-17α-ethynylandrostan-17β-ol-3-one was prepared by treating 4α,5α - epoxy - 17β - hydroxy - 17α - ethynylandrostano[2,3-d]isoxazole with sodium methoxide, and was obtained in the form of rhomboids, m.p. 238.0—240.0°C. (dec.) (corr.) when recrystallized from methyl ethyl ketone; $[\alpha]_D^{25} = +59.0°$ (1% in pyridine).

Example 4.

a) 4α,5α - Epoxy - 17β - hydroxy - 17α-methylandrostano[2,3 - d]isoxazole, m.p. 214.2—218.6°C. (corr.) (recrystallized from benzene), $[\alpha]_D^{25} = +80.7°$ (1% in chloroform), was prepared by treating 17β-hydroxy - 17α - methyl - 4 - androsteno-[2,3-d]isoxazole with maleic anhydride and hydrogen peroxide in methylene dichloride solution.

b) 2α - Cyano - 4α,5α - epoxy - 17α-methylandrostan - 17β - ol - 3 - one was prepared by treating 4α,5α - epoxy - 17β-hydroxy - 17α - methylandrostano[2,3 - d]-isoxazole with sodium methoxide, and had the m.p. 246.0—246.5°C. (dec.) (corr.) when recrystallized from a dioxane-benzene mixture; $[\alpha]_D^{25} = +122.9°$.

WHAT WE CLAIM IS:—

1. A 2α - cyano - 4α,5α - epoxy - 3 - oxo-androstane steroid, the steroid moiety having from nineteen to twenty-three carbon atoms exclusive of ester radicals, or a salt thereof.

2. 2α - Cyano - 4α,5α - epoxyandrostan-17β-ol-3-one.

3. 17β - Acetoxy - 2α - cyano - 4α,5α-epoxyandrostan-3-one.

4. 2α - Cyano - 4α,5α - epoxy - 17α-ethynylandrostan-17β-ol-3-one.

5. 2α - Cyano - 4α,5α - epoxy - 17α-methylandrostan-17β-ol-3-one.

6. A process for preparing a 2α - cyano-4α,5α - epoxy - 3 - oxo - androstane steroid or a salt thereof, which comprises treating with a strong base the corresponding 4α,5α-epoxy - steroido[2,3-d]isoxazole, the steroid moiety having from nineteen to twenty-three carbon atoms exclusive of ester radicals, and, if desired, acidifying the resulting salt of the 2α - cyano - 4α,5α - epoxy - steroid to obtain the free product.

7. A process according to claim 6, wherein the 4α,5α - epoxy - steroido[2,3 - d]isoxazole is prepared by treating a Δ^4-steroido[2,3-androstane-d]isoxazole with an oxidizing agent capable of converting an olefinic double bond to an epoxide.

8. A process according to claim 6 for preparing 2α - cyano - 4α,5α - epoxyandrostan-17β-ol-3-one, wherein 17β - hydroxy - 4α,5α-epoxyandrostano[2,3-d]isoxazole or a 17-carboxylic acid ester thereof is treated with the strong base.

9. The process for preparing a 2α - cyano-4α,5α - epoxy - 3 - oxo - androstane steroid or a salt thereof substantially as herein described with reference to the Examples.

10. A compound prepared by the process according to any one of claims 6 to 9.

11. A compound according to claim 1 as herein described.

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